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# EDITORIAL

**On these pages the editor offers his opinions, unshackled by advertising patrons and unrestrained by anything save a sense of the decent and the truthful. The editor, alone, is responsible for their type, their tone and their tenor.**

## THE 1940 PHARMACOPOEIAL CONVENTION

THE following editorial originally appeared in the May, *1930,* issue of this JOURNAL. It is now reprinted because it is again as timely and pertinent as it was when originally written.

The president of the Board of Trustees has issued the call for the 1940 Convention at Washington, and it is highly desirable, especially in view of certain administration policies, that Pharmacy at the proper time will present a broad, dignified, unified stand at this meeting.

"Every decennium—on the decennium—the Convention of the United States Pharmacopœia foregathers in Washington in order to prepare a revision of that important book of standards.

The 1930 Convention has come and gone. A new Committee of Revision was chosen, and as chosen, evidenced sufficient sound sense to elect for its chairman the same gentleman who had so wisely and so efficiently served in that capacity during the preceding decennium.

Yet before the wise thing was done the body pharmaceutic suffered many a convulsion.

It seems that coincident with these pharmacopœial conventions the body pharmaceutic breaks out in a fearful rash.

Nor is this rash so sudden. For long before the cohorts meet at Washington evidences of infection are most apparent.

A general uneasiness throughout the body—erratic rises in temperature, a relative and absolute increase in meddlesome leukocytes, attacks of insomnia, gatherings here and there, profuse and unnecessary sweating, incoherency of speech, incoordination of effort—these are the pre-conventional symptoms that positively point to the coming fever and rash.

Petty politics, engineered by pettier politicians, masquerading as scientists; geographic conceits fostered by prejudiced provincials, and unbridled ambitions hard-ridden by a crowd of incompetents—these are the unpleasantnesses of a pharmacopœial convention.

'Physicians should dictate the medical or therapeutic scope of the Pharmacopœia.'

That was the intelligent viewpoint of the experienced chairman of the Revision Committee.

And that seems to be the only fair and sane viewpoint.

Yet with this moot question, as with a good many others, certain pharmaceutic 'experts' voiced a lack of faith in the competence of medical authorities to handle even their own specific medical problems.

Nor did this attitude assist any in the furtherance of harmony between the medical and the pharmaceutical groups in attendance upon the convention.

Indeed, it became necessary to effect a fusion of the medical group with the saner stratum of the pharmaceutical group in order to carry through certain plans which would insure a wise guidance of pharmacopœial progress during the next ten years.

It seems certain that unless Pharmacy presents a saner and a more united front at the convention ten years hence—it may well be that the organization of medicine with headquarters at Chicago, aided and abetted by governmental bureaus, will take away from organized Pharmacy its beloved Pharmacopœia, the last real stronghold of professionalism it possesses.

IVOR GRIFFITH."

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**Casein and Zein as New Soap Additives.** P. I. Smith. *The American Perfumer 38,* 39 (1939). Casein as a soap filler affords economical manufacture, better lathering power and less alkalinity. Powdered casein may be added during saponification so that the soluble caseinates can be fully absorbed. To overcome the difficulty of the protein taking up some of the needed alkali, a process has been devised preparing casein with an acid reaction. A practical method of adding very finely ground casein is to mill it with soap shavings.

Zein, a new product derived from maize, increases the lathering properties of soap, in addition to giving it more body. This is helpful in the economical use of fats. Zein may be added during the mixing process in a 25 per cent. alcoholic solution containing 5 per cent. glycerin. J. E. K.

# ORIGINAL ARTICLES

## ALKALOIDS AND THEIR REAGENTS

By Charles C. Fulton

Associate Chemist, Alcohol Tax Unit, U. S. Treasury Department
St. Paul, Minnesota

IDENTIFICATION, by recognition of characteristic crystals under the microscope, is used increasingly for alkaloids, with great success. The reagents are applicable in the same way to amines in general.

There are, however, so many reagents. The writer has previously published a list of ninety-one reagent formulas (1), and has now prepared an article containing ninety-three more. If the reagents are not to be unmanageable from mere number some means must be devised for handling them, or a selection made of a comparatively small number for ordinary use. We could strike some of small value from the lists, but at least 100 reagents will justify themselves in many different ways.

A few reagents are mentioned over and over again in the textbooks as the traditional "general alkaloidal reagents." Some chemists apparently prefer to confine themselves to these even when better tests for the same alkaloids are already known. There is a temporary advantage in this use of those reagents and tests that have been most thoroughly studied, particularly those for which photographs of the crystals are given in Stephenson's book (2) or other sources. But such a limitation cannot be defended as a permanent policy.

It might be possible to select from the whole field of reagents the best ten or twelve for general use, although anyone who tries to do so is more likely to find himself with the best thirty or forty. There can be little doubt as to the best precipitating compounds for characteristic crystals: these are $KI_3$ and the chloro- and bromo-acids of gold and platinum. Each of these five compounds, however, makes several distinct reagents. At least three or four different

forms of Wagner's reagent, with different amounts of KI in proportion to the iodine, are absolutely necessary to obtain the different characteristic crystals. The halogen acids of gold and platinum, ordinarily used in plain water, give different results—and many beautiful and necessary crystal tests—with an excess of HCl present, or in concentrated HCl, strong acetic acid, or syrupy $H_3PO_4$.

The limitation project, in fact, is almost certain to break down; first, because in all probability every author and nearly every chemist will have one or more favorite reagents outside the limited group; second, because even the *best* ten or twelve reagents (supposing we could agree on them) will not give tests for all pure alkaloids, and in many other cases will not include the best test for a given alkaloid; and finally, because no chemist who has learned to use 100 reagents will consent to confine himself to ten.

The only remedy is to learn to use 100 reagents, or whatever number may finally be found desirable. Fortunately the solution is simple.

It consists in (a) making the tests on dilute solutions of the alkaloid, so that a little material goes a long way; (b) dividing the reagents into groups and ranking them so that tests on an unknown with three or four reagents will show which of the other reagents are sensitive to that particular amine and which are not; and (c) dividing the alkaloids into corresponding groups and arranging them in order so that sensitivity tests will yield a tentative identification, whereupon a suitable reagent for microcrystals can then be tried.

A preliminary statement of the method was given in the writer's first article on the subject, "The Identification of Alkaloids by Precipitation" (3).

Phosphomolybdic acid gives a convenient standard for dilute solutions. A little of the alkaloidal salt is dissolved in water, or the alkaloid is dissolved in dilute acid, preferably sulfuric, and a portion of the solution is taken for further dilution. By repeatedly doubling the volume of portions, the most dilute solution is found which will still give a distinct precipitate with phosphomolybdic acid. This is "solution 1"; the next stronger solution (containing twice as much alkaloid) being "solution 2," while the next weaker (with half as much alkaloid) is "solution ½." The sensitivity of any reagent rela-

tive to phosphomolybdic acid can then be found from such a series of solutions, and the relative amount of alkaloid required for precipitation specified. However, the primary tests of classification are made on solution 1.

The ordering of reagents is not difficult. If Marme's reagent, for example, gives a precipitate, it is certain that Mayer's, Wagner's and Dragendorff's reagents will also precipitate; and if it does not, neither will zinc potassium iodide, palladium chloride, or gold cyanide. By tests on solution 1 (with various alkaloids) all the reagents can be ranked, with very few anomalies and inconsistencies.

In the same way an alkaloid is given a position relative to the others by determining which reagents will precipitate it in solution 1.

**Table 1**

Table 1 presents a tentative classification of the reagents and alkaloids, together with a few other amines.

The first column gives the order of reagents, beginning with those sensitive to the greatest number of alkaloids.

The second column gives the order of strong bases, beginning with the most difficult to precipitate. These are precipitated in solution 1, in general, by the reagents standing above them and not by those lower in the list.

In the third column are the weak bases; while the fourth column gives some variations in the reagents or in their rank when used on these weak bases.

The data are very far from complete or exact for some of the alkaloids listed, hence some may be a little out of place. However, the table will probably have more value by the inclusion of as many alkaloids as possible, even if it is not correct in all details.

Occasional inconsistencies as found in practice are most often due to oxidation and are especially noticeable with bromine water and gold chloride.

The alkaloids near each other in the table are more or less related in various ways, and in the earlier article (3), to which reference can be made, were put in groups rather than in a double column.

TABLE No. 1.

| | | | |
|---|---|---|---|
| Phosphotungstic acid | | | |
| Phosphomolybdic acid | | | |
| | Hydroxylamine | Theophylline | |
| | Ammonia | Theobromine | |
| | Potassium | Ecgonine | |
| | Ephedrine | | |
| Wagner's No. 1 | | Betaine | |
| | Beta Eucaine | | Acid Wagner's No. 1 |
| Br in NaBr | | | Acid Dragendorff's |
| | Alpha Napthyl-amine | Antipyrine | |
| | | Aniline | |
| | Beta Naphthyl-amine | Benzoyl Ecgonine | Br in HBr |
| Dragendorff's | | | |
| | Hexamethylene-tetramine | Caffeine | |
| | | Colchicine | |
| | Pyridine | | |
| | Piperidine | | |
| | Arecoline | | |
| | Pilocarpidine | | |
| | Pyrrolidine | | |
| | Cytisine | | |
| | Coniine | | |
| Silicotungstic acid | | | |
| | Scopolamine | | |
| Valser's reagent | | | |
| | Morphine | | Acid Mayer's |
| Wagner's No. 4 | | | Acid Wagner's No. 4 |
| | Pilocarpine | | |
| | Stovaine | | |
| Bromine water | | | |
| | Hysoscyamine | | |
| Gold Bromide | | | |
| | Nicotine | | |
| | Physostigmine | | |
| | Atropine | | |
| | Dionine | | |
| | Homatropine | | |
| Gold Chloride | | | |
| | Novocaine | | |
| | Codeine | | |
| Platinum Na Thiocyanate | | | |
| Mercuric Na Bromide | | | |
| Wagner's No. 8 | | | Acid Wagner's No. 8 |
| Mercuric K Thio-cyanate | | | |
| Zinc Na Thiocyanate | | Peptone | |
| Bromomercuric acid | | | |
| | Alpha Eucaine | | |
| Mayer's & KI | | | Picric acid |
| Gold Br & HCl | | | Gold Br & HCl |
| Marme's reagent | | | Mercuric Na Bromide |
| Tannin & Na acetate | | | |
| Stannous H Iodide | | | |
| | Heroine | Narceine | |

| | | | |
|---|---|---|---|
| Gold Cl & HCl | | | |
| | Cocaine | | |
| | Cotarnine | Solanine | |
| | Hydrastinine | Berberine | |
| Picric acid | | | Mercuric K Thiocyanate |
| Molybdic acid | | | |
| | Sparteine | | Zinc Na Thiocyanate |
| | Yohimbine | Piperine | |
| | Aconitine | | Mayer's & KI |
| | | | Marme's |
| Na Phosphomolybdate | | Aspidospermine | |
| | Thebaine | | Tannin & Na acetate |
| Mercuric Na Chloride | | Apocodeine | |
| | Peronine | | $K_2CrO_4$ |
| | Cinchonine | | $Na_2HPO_4$ |
| Platinum Bromide | | Apomorphine | |
| Palladium Chloride | | Corydaline | |
| | Cinchonidine | | Concd K Acetate |
| | Quinine | | Mercuric Na Chloride |
| | Quinidine | Pseudomorphine | |
| Chloromercuric acid | | | NaOH |
| | Lobeline | | $Na_2CO_3$ |
| Platinum Chloride | | | $NH_4OH$ |
| | Brucine | | KCN |
| NaOH | | | Chloromercuric acid |
| $Na_2CO_3$ | | Hydrastine | |
| $NH_4OH$ | | Narcotine | |
| KCN | | | Palladium Chloride |
| | Strychnine | | Platinum Chloride |
| Mercuric Na Chloronitrite | | | $CrO_3$ |
| | | Papaverine | |
| Platinum Cyanide | | | K Ferricyanide |
| Gold Cyanide | | | Na Nitroprusside |
| $CrO_3$ | | | Perchloric acid |
| Mercuric Na Nitrite | | | $HgCl_2$ |
| $BiCl_3$ in HCl | | | K Ferrocyanide |
| $SnCl_4$ in HCl | | | $ZnCl_2$ |
| Zinc K Iodide | | Fuchsine | |
| K Ferricyanide | | | $BiCl_3$ in HCl |
| Nickel Na Thiocyanate | | Malachite Green | |
| $ZnCl_2$ & HCl | | | $SbCl_3$ in HCl |
| Na Saccharate | | | $ZnCl_2$ & HCl |
| | | | $SnCl_2$ & HCl |
| | | | $FeCl_3$ in Concd HCl |

## Identification of an Alkaloid

As an illustration of identification, suppose we have an unknown alkaloid which we dissolve in dilute acid, obtain solution 1, and test with Marme's reagent and zinc Na thiocyanate. Precipitates with these reagents show that the alkaloid is not among those in the upper part of the table, down to codeine at least. If we now find that picric acid and molybdic acid also precipitate from solution 1, but

that palladium chloride, platinum bromide, and mercuric Na chloride do not, all but a few alkaloids are eliminated from further consideration. If we suspect yohimbine, we can now identify it with a microscopic test, using gold cyanide, which gives delicate needles in sheaves in solution 1 after standing a short time.

Even if we first test for other alkaloids adjacent to yohimbine in Table 1, sparteine with gold chloride and aconitine with permanganic acid (tests also successful in solution 1, although a little greater concentration as in solutions 2 to 4 is better), and perhaps make still other tests, we are not following a hit or miss procedure, but one which leads directly to definite results and requires only a few milligrams of the alkaloid. Solution 1 in the case of yohimbine is approximately 1:1600, so that 1 mg. will make 1.6 cc. of solution 1; and each test with a precipitating agent requires only one drop of solution.

The following abbreviated table of sensitivities (Table No. 2) shows the nature of the essential facts in regard to the precipitation of yohimbine.

TABLE No. 2

*Yohimbine* (in dilute $H_2SO_4$)

| | |
|---|---|
| Mercuric Na Bromide—½ | Mercuric Na Chloride—4 |
| Zinc Na Thiocyanate—½ | Chloromercuric acid—4 |
| Stannous H Iodide—½-1 | Platinum Bromide—2 |
| Marme's reagent—1 | Palladium Chloride—4 |
| Picric acid—1 | $Na_2CO_3$—4-8 |
| Molybdic acid—1 | $CrO_3$—4 |
| | Platinum Cyanide—2-1 |
| | *Gold Cyanide*—2 (½) |

We need, of course, tables of sensitivities for all the alkaloids that we are likely to meet with in pure form; tables which will also show what reagents will yield characteristic crystals, particularly from dilute solution.

Such tables of sensitivities with a large number of reagents have been published for cocaine and novocaine (4), and heroine (5), and prepared for morphine (6).

Although the writer has prepared short tables for numerous other alkaloids at different times, the continual expansion of the number of reagents that must be taken into consideration has constantly made earlier results inadequate.

## How to Test Reagents

A compound which may be a precipitating agent is tried out first on papaverine. If it is not at least moderately sensitive to papaverine it will not precipitate most alkaloids at all, and cannot be of value as a general reagent. Sensitive reagents for papaverine include even the weak basic reagents, which will not precipitate strong alkaloids, unless from quite concentrated solution.

Strychnine is probably the most easily precipitated of all strong alkaloids and gives crystals with most reagents. If a crystal test is obtained with a reasonably dilute strychnine solution, the compound can be accepted as an alkaloidal reagent of some value for both precipitation and crystals.

Neither papaverine nor strychnine shows remarkable absolute sensitivity; they are, however, reasonably sensitive to a greater number of reagents than other alkaloids.

When a compound is sensitive to these two alkaloids it is desirable to learn to what other alkaloids it is sensitive and about where it stands with respect to other reagents. This is easily accomplished by testing representative alkaloids; for instance cinchonine, cocaine, novocaine, scopolamine and ephedrine might be used, giving a series increasingly difficult to precipitate. The results show roughly where the reagent would belong in Table 1.

Tropococaine is another alkaloid that may be used in determining whether the reagent is likely to give any useful crystals, for it forms crystals with most reagents that will precipitate it.

Bases near the top of Table 1 have to be tested with the most general reagents; and moreover the most general reagents are more likely to give crystals when the compounds do not reach an extreme insolubility. Hence the final value of a very general reagent, such as a complex oxygen acid, may have to be ascertained chiefly by tests on the simpler bases, those most difficult to precipitate.

When a reagent is made by combining two or more compounds, the formula for greatest sensitivity is best discovered by trials on some alkaloid to which it is sensitive, but not quite as sensitive as phosphomolybdic acid. If, for example, the maximum sensitivity of a compounded reagent to a particular alkaloid is two phosphomolybdic acid units, with variation of the formula such as doubling or halving the quantity of one of the components, four, eight or sixteen units may then be required for precipitation. After determining the em-

pirical formula for the most sensitive form, approximately or within limits, it can then be seen whether this corresponds to some recognizable compound; for example $NaHgCl_3$ with $HgCl_2$ and NaCl, or $K_2CdI_4$ with $CdI_2$ and KI.

In considering crystals it is especially necessary to try, also, forms of the reagent with an excess of the "dissolving component," as $HgI_2$ with more than enough KI to hold it in solution ("Mayer's and KI" reagent), $NaHgCl_3$ with excess NaCl, etc.

It is also desirable to try the effect on crystal formation of various acids, particular HCl with the precipitating agents which are double salts of metals.

Often the study of a particular alkaloid brings about the development of a modified reagent formula, usually less sensitive than the standard form but valuable for crystals, and this when tried on other alkaloids proves to be of general value.

## Summary and Conclusions

1. In order to make completely effective use of crystal tests for alkaloids, we are confronted with the necessity of using a large number of reagents, probably at least 100.

2. A plan is proposed for using the reagents systematically, for classifying the alkaloids and facilitating their identification, by making tests of classification on the most dilute solution yielding a distinct precipitate with phosphomolybdic acid.

3. A table is given, showing the order of reagents in respect to precipitating power; the order of the alkaloids and their division into strong and weak bases; and the relations between reagents and alkaloids observed in testing dilute solutions containing one "phosphomolybdic-acid unit" of alkaloid.

4. The writer does not claim that his method of classifying and identifying an alkaloid must always be followed exactly and in detail. Knowledge of the ranking of reagents and alkaloids, and of their relations to each other (as given in Table 1) will largely eliminate random trials, whatever plan or system is used.

5. The methods of testing new or proposed reagents for effectiveness and value, and of determining suitable formulas, are given.

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2. Charles H. Stephenson: Some Microchemical Tests for Alkaloids. Including Chemical Tests of the Alkaloids Used, by C. E. Parker. J. B. Lippincott Co., 1921.

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4. Charles C. Fulton: The Identification of Cocaine and Novocaine. *Am. J. Pharm.*, July and August, 1933.

5. G. D. Williams and C. C. Fulton: The Microscopic Identification of Heroine. *Am. J. Pharm.*, September, 1933.

6. Charles C. Fulton: The Identification of Morphine by Chemical Tests (a mongraph—unpublished).

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**Synthetic Antimalarials.** W. O. Kermack. *Chemical Products 2*, 5 (1939). It is estimated that the annual toll from malaria is ten million of the world's inhabitants. The disease may be prevented by destroying infectious mosquitoes or preventing their bites. Acute attacks of the disease may be treated with quinine. Unfortunately, this chemo-therapeutic agent does not always effect a complete cure, and much personal distress and social inefficiency result from chronic and debilitating forms of the dread disease.

Thus, the relative failure of quinine, and the complicated history of the malarial parasite in the human body demands study and research for newer and better curative compounds. A new technique for testing antimalarials has been developed, using canaries and related birds. Those substances showing promise through these quick tests may be examined further and more completely. Plasmoquine resulted from this technique. Atebrin was also found by German scientists in this manner. Their high toxicity, however, withheld their general use.

Further work on these substances, introducing modifications in the molecular structure, has resulted in a promising substance with antimalarial properties with a formula half way between quinine and atebrin, and a name which has not yet been determined. A second substance with these qualities is undecylmethylene diamidine. A third is 4-(6-methoxyquinolyl)-a-piperidyl carbinol.

The value of these synthetics in actual practice has not yet been determined, but it is hoped that they, or some similar substances may be the long-sought, ideal medications. J. E. K.

# HYDROGEN ION CONCENTRATION AND CYANOGENESIS IN SORGHUM

By James F. Couch and Reinhold R. Briese

Contribution from the Pathological Division, Bureau of Animal Industry, Washington, D. C.

(Continued from April Issue)

Although this series of experiments is not strictly comparable with those on Johnson grass because the proportion of added acid solution to dry matter is here much larger, the general results observed do not differ significantly. The fresh plant appears to show a weaker buffer action but this is undoubtedly due to the greater volume of acid used.

The Spur feterita samples showed the same tendency as those of Johnson grass and hegari to become more acid on twenty-four hours' maceration when mixed with low concentrations of acids and to become more alkaline when mixed with higher concentrations of acid. The alkaline shift is not so pronounced and appeared later. With the tartaric acid series none of the mixtures developed a pH greater than the initial pH although the tendency towards alkalinity with increasing acid concentration is evident (Tables 17 to 20, inclusive).

The effective concentrations of added acids are similar to those observed with Johnson grass and hegari. Small concentrations of the acids increased or did not diminish the yield of HCN; larger concentrations tended to decrease the yield of HCN. The largest yields of HCN were obtained after additions of 0 to 0.2 g./liter of hydrochloric acid, of 0 to 0.3 g./liter of sulfuric acid, and 0.1 to 0.4 g. of tartaric

TABLE 16.—Optimum pH range for Spur feterita with different acids.

| Coll. No. | Acid | pH range | HCN |
|---|---|---|---|
| | | | mg% |
| 47–37 | Hydrochloric | 4.15 to 4.92 | 8.5 to 8.9 |
| 80–37 | Hydrochloric | 3.47 to 4.53 | 22.4 to 22.9 |
| 50–37 | Sulfuric | 4.28 to 4.89 | 8.5 to 8.9 |
| 34–37 | Tartaric | 4.50 to 5.04 | 13.5 to 14. |

TABLE 17.—Hydrocyanic acid produced by fresh Spur feterita leaves in hydrochloric acid at different pH. Weight of plant samples, 100 g. Volume of acid added, 325 cc. Plant sample 47–37.

| Concn. of acid | pH | | | | HCN, calcd. to fresh plant |
|---|---|---|---|---|---|
| g/liter | Start | After 24 hours | Change | Average | mg% |
| 0. | 5.58 | 4.26 | —1.31 | 4.92 | 8.7 |
| 0.1 | 5.15 | 4.23 | —0.92 | 4.69 | 8.9 |
| 0.2 | 4.87 | 4.10 | —0.77 | 4.48 | 8.7 |
| 0.3 | 4.32 | 4.14 | —0.18 | 4.23 | 8.4 |
| 0.4 | 4.37 | 3.93 | —0.44 | 4.15 | 8.5 |
| 0.5 | 3.99 | 3.98 | —0.01 | 3.98 | 8.1 |
| 0.7 | | 3.81 | | | 7.4 |
| 1.0 | 3.26 | 3.40 | 0.14 | 3.33 | 6.2 |

TABLE 18.—Hydrocyanic acid produced by fresh Spur feterita leaves in hydrochloric acid at different pH. Weight of plant samples, 100 g. Volume of acid added, 300 cc. Plant sample 80–37.
(1) $HgCl_2$ not added.

| Concn. of acid | pH | | | | HCN, calcd. to fresh plant |
|---|---|---|---|---|---|
| g/liter | Start | After 24 hours | Change | Average | mg% |
| 0. | 5.52 | 4.13 | —1.39 | 4.83 | 24. (1) |
| 0.1 | 5.01 | 4.05 | —0.96 | 4.53 | 22.9 |
| 0.2 | 4.63 | 4.03 | —0.60 | 4.33 | 22.1 |
| 0.3 | 4.06 | 3.97 | —0.09 | 4.06 | 22.2 |
| 0.4 | 3.97 | 3.99 | 0.02 | 3.98 | 21.8 |
| 0.5 | 3.65 | 4.05 | 0.40 | 3.85 | 21.8 |
| 0.7 | 3.01 | 3.92 | 0.91 | 3.47 | 22.4 |

TABLE 19.—Hydrocyanic acid produced by fresh Spur feterita leaves in sulfuric acid at different pH. Weight of plant samples, 100 g. Volume of acid added, 325 cc. Plant sample 50–37.

| Concn. of acid | pH | | | | HCN, calcd. to fresh plant |
|---|---|---|---|---|---|
| g/liter | Start | After 24 hours | Change | Average | mg% |
| 0. | 5.57 | 4.22 | —1.53 | 4.89 | 8.9 |
| 0.1 | 5.25 | 4.11 | —1.14 | 4.68 | 8.9 |
| 0.2 | 5.07 | 4.04 | —1.03 | 4.55 | 8.7 |
| 0.3 | 4.90 | 4.02 | —0.88 | 4.46 | 8.7 |
| 0.4 | 4.61 | 3.95 | —0.66 | 4.28 | 8.5 |
| 0.5 | 4.33 | 3.95 | —0.38 | 4.14 | 8.4 |
| 0.7 | 3.43 | 4.02 | 0.49 | 3.72 | 8.4 |
| 1.0 | 3.39 | 3.77 | 0.38 | 3.58 | 8.0 |

TABLE 20.—Hydrocyanic acid produced by fresh Spur feterita leaves in tartaric acid at different pH. Weight of plant samples, 100 g. Volume of acid added, 325 cc. Plant sample 34–37.

| Concn. of acid | pH | | | | HCN, calcd. to fresh plant |
|---|---|---|---|---|---|
| g/liter | Start | After 24 hours | Change | Average | mg% |
| 0. | 5.66 | 4.42 | —1.24 | 5.04 | 13.6 |
| 0.1 | 5.42 | 4.34 | —1.08 | 4.88 | 13.8 |
| 0.2 | 5.19 | 4.30 | —0.89 | 4.74 | 13.9 |
| 0.3 | 5.10 | 4.26 | —0.84 | 4.68 | 14.0 |
| 0.4 | 5.01 | 4.24 | —0.77 | 4.62 | 13.9 |
| 0.5 | 4.85 | 4.14 | —0.71 | 4.50 | 13.5 |
| 0.6 | 4.59 | 4.10 | —0.49 | 4.34 | 12.5 |
| 1.0 | 4.45 | 4.07 | —0.38 | 4.26 | 12.3 |

acid. Addition of 0.1 per cent. acid decreased the HCN yield by 30 per cent., 10 per cent. and 12 per cent. in the cases of hydrochloric, sulfuric and tartaric acids, respectively. This was much less repression than occurred with Johnson grass in spite of the larger ratio of acid.

The optimum pH ranges as found are presented in Table 16. These are uniformly lower than the corresponding figures for Johnson grass, but agree fairly closely with those for hegari.

Differences between young and older plants are shown by the experiments on numbers 47-37 and 80-37 collected eight weeks apart. The first sample was grown in the same field but in a different location from the latter and was planted a month earlier. There was, therefore, a four weeks' difference in actual age but a greater difference in maturity owing to the more rapid growth of the later crop. No. 80-37 had a weaker buffering action than 47-37 in spite of a greater content of dry matter. Parallel with this the optimum pH range is lower and there is little or no repression of the HCN yield with the concentrations used. While there is a decrease of nearly 17 per cent. between the maximum HCN yield and that obtained with 0.07 per cent. acid in the case of No. 47-37 the corresponding differences in the case of No. 80-37 are within experimental error.

### Effect of Higher Concentrations of Acid on the Same Plant Sample

The experiments already cited were made on different collections of the fresh plants and each single collection was used with one acid only. The results were not so directly comparable as they would have been had all the determinations been made with the same sample since there were differences of HCN content and moisture between the various samples. To remedy this condition a series of experiments was made on a sample of fresh hegari to which were added solutions of surfuric, hydrochloric, tartaric, and oxalic acids. To obtain some information concerning the effects of higher concentration these acids were added in the proportion of 2.5 and 5 g. per liter. In one series the proportion of added acid to plant was kept at the same point as in the previous experiments, that is, 300 cc. to 100 g., or 3 to 1. In the second series the proportion of acid was increased to 400 cc. to 50 g. of plant, or 8 to 1.

TABLE 21.—Hydrocyanic acid produced by fresh hegari leaves in different acids at two concentrations. Weight of plant sample, 100 g. Volume of acid solution, 300 cc. Plant sample 65–38.

| Acid | Concn. g/liter | pH | | | | | HCN | |
|---|---|---|---|---|---|---|---|---|
| | | Acid | Start | After 24 hours | Change | Aver-age | Calcd. to fresh plant | Percent. of unacidified |
| | | | | | | | mg% | |
| Water alone | | | 5.70 | 4.18 | —1.52 | 4.94 | 13.7 | 100. |
| Sulfuric | 2.5 | 1.35 | 2.58 | 3.29 | 0.71 | 2.32 | 2.8 | 20. |
| Sulfuric | 5 | 1.11 | 1.38 | 1.68 | 0.3 | 1.58 | 2.2 | 16. |
| Hydrochloric | 2.5 | 1.07 | 1.43 | 2.00 | 0.57 | 1.72 | 2.7 | 20. |
| Hydrochloric | 5. | 0.76 | 0.98 | 1.10 | 0.12 | 1.04 | 2.3 | 17. |
| Tartaric | 2.5 | 2.32 | 3.77 | 3.97 | 0.20 | 3.87 | 7.3 | 53. |
| Tartaric | 5. | 2.13 | 3.19 | 3.40 | 0.21 | 3.30 | 4.8 | 35. |
| Oxalic (1) | 2.5 | 1.58 | 2.41 | 1.41 | —1.00 | 1.91 | 3.9 | 28. |
| Oxalic (1) | 5. | 1.35 | | | | | 2.7 | 20. |

(1) As anhydrous oxalic acid.

TABLE 22.—Hydrocyanic acid produced by fresh hegari leaves in large volumes of different acids at two concentrations. Weight of plant sample, 50 g. Volume of acid solution, 400 cc. Plant sample 62–38.

| Acid | Concn. g/liter | pH | | | | HCN | |
|---|---|---|---|---|---|---|---|
| | | Start | After 24 hours | Change | Aver-age | Calcd. to fresh plant | Percent. of unacidified |
| | | | | | | mg% | |
| Water alone | | 5.86 | 4.19 | —1.67 | 5.08 | 11.4 | 100. |
| Sulfuric | 2.5 | 1.81 | 1.72 | —0.09 | 1.77 | 2.9 | 25. |
| Sulfuric | 5 | 1.34 | 1.27 | —0.07 | 1.30 | 3.0 | 25. |
| Hydrochloric | 2.5 | 1.38 | 1.27 | —0.11 | 1.33 | 2.7 | 23. |
| Hydrochloric | 5. | 0.95 | 0.86 | —0.09 | 0.90 | 3.4 | 29. |
| Tartaric | 2.5 | 3.27 | 3.32 | 0.05 | 3.30 | 7.1 | 62. |
| Tartaric | 5. | 2.86 | 3.14 | 0.28 | 3.00 | 5.2 | 45. |
| Oxalic (1) | 2.5 | 2.16 | 2.17 | 0. | 2.17 | 5.2 | 45. |
| Oxalic (1) | 5. | 1.64 | 1.61 | —0.03 | 1.63 | 4.4 | 38. |

(1) As anhydrous oxalic acid.

The results are presented in Tables 21 and 22. The addition of acid in concentrations indicated markedly repressed the cyanogenetic process, the effect being roughly in the order of the dissociation constant of the acid. In the first series (Table 21) sulfuric and hydrochloric acids in 2.5 g. per liter concentration reduced the HCN yield 80 per cent. and in 5 g. per liter concentration, 84 and 83 per cent., respectively. In the latter concentration oxalic acid reduced the HCN yield 80 per cent. and tartaric acid 65 per cent. In the second series where the ratio of acid to plant was much greater the per cent. of repression was somewhat smaller with all four acids. This may be explained as due to the hydrolizing effect of stronger acid on the nitrile glucoside during the process of distilling the HCN, resulting in the formation of more HCN than can be attributed to the enzymolysis alone.

## Summary

The effect of hydrogen ion concentration on cyanogenesis in sorghum has been measured with dried Johnson grass and with fresh hegari and Spur feterita using hydrochloric, sulfuric, and tartaric acids with all three types of sorghum and, in addition, acetic and oxalic acids with Johnson grass.

Cyanogenesis was stimulated by small concentrations of these acids and repressed with higher concentrations, 0.5 to 1.0 g. per liter, the effect being roughly proportional to the dissociation constant of the acid. Concentrations of 2.5 to 5 g. per liter repressed cyanogenesis as much as 84 per cent. The quantity of hydrocyanic acid produced was correlated with the hydrogen ion concentration. The character of the added acid has little effect.

The pH ranges in which there was optimum production of hydrocyanic acid did not vary significantly for the different acids. The optimum ranges were similar for hegari (4.12-4.86), and Spur feterita (4.10-4.86), and somewhat higher for Johnson grass (5.04-5.16).

The pH of mixtures of the acids and plant tissues changed regularly during the twenty-four-hour period of the experiment. The average of the initial and twenty-four-hour pH values were nearly identical with the average for the whole period. With small concentrations the mixtures tended to become more acid during the twenty-four-hour period; with higher concentrations this tendency was reduced and the mixtures became more alkaline.

Sorghum exhibits a buffering action against the acids used and this was more pronounced with fresh than with dried plants.

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# REPRINTED ARTICLE

## SOME ASPECTS OF FIFTY YEARS' PROGRESS IN PHARMACEUTICAL AND RELATED SCIENCES

**(Concluded from the April Issue)**

The period under review has seen tremendous growth in the field of organic chemistry, not only in the subject itself, but also in its application to medicine and pharmacy. An excellent review of some of the major contributions of organic chemistry to pharmacy was made by Sissons in his presidential address to this section in 1926, but further important advances have been made since that time.

Considering firstly the question of active principles, much had already been done in the isolation of the active principles of vegetable drugs. The 1885 Pharmacopœia contained some twenty-two active principles, including fourteen alkaloids (nine of which are still official) and eight other substances, of which seven are now official. The principal additions to these include the alkaloids hyoscine (added in 1898), pelletierine and theobromine (1914), emetine, ephedrine, ergotoxine and quinidine (1932), and theophylline and ergometrine (1936), together with the mixture of glycosides, strophanthin (1932).

The development of satisfactory methods of quantitative organic analysis has done much, as has already been pointed out, in providing the pharmacist and medical man with standardized preparations.

It is principally in the field of synthetic organic chemistry, however, that medicine and pharmacy have benefited most. The 1885 pharmacopœia contained only about a dozen substances which might be considered synthetic, including salicylic acid, ether and ethyl acetate, amyl nitrite and Spirit. Aether. Nit., chloral hydrate and butyl chloral hydrate, chloroform and iodoform, apomorphine, nitroglycerin, pyroxylin and salts of phenolsulphonic acid. The period following 1885 was marked by great activity in the field of synthesis, not only of natural products, such as cocoaine, menthol, caffeine, atropine and camphor, but also of a great variety of other substances.

From a medicinal point of view, the antipyretics and hypnotics were the most numerous of the earlier additions, acetanilide, paraldehyde, phenacetin, phenazone and sulphonal being included in the 1890 Additions to the Pharmacopœia. The edition of 1898 made few alterations, but the 1914 B. P. included aspirin, barbitone, methyl-sulphonal and chloral formamide, whilst that of 1932 added amidopyrine, sodium barbitone, phenobarbitone and its sodium salt, carbromal and chlorbutanol to these groups.

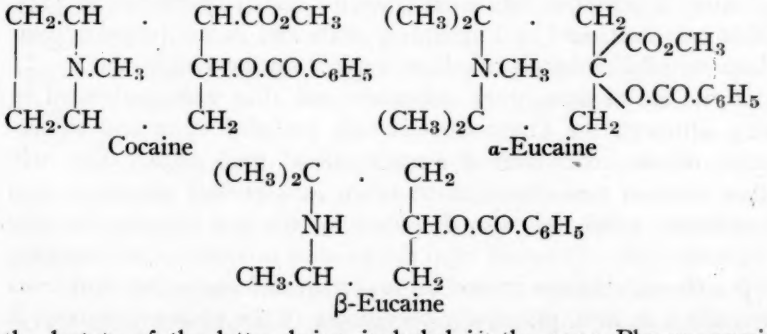
Progress in the field of anaesthetics has been somewhat irregular. The first observation of anaesthesia produced by inhalation of gases appears to have been made in 1799 by Humphry Davy, then a young man of twenty-one, who, working as assistant to Beddoes, noted the anaesthetic properties of nitrous oxide. In the following year, Beddoes showed that ether possessed similar properties, and at about the same time Davy suggested that nitrous oxide might be used for minor operations. It was not until 1842, however, that either was used as an anaesthetic for surgical purposes, the credit for this generally being given to the American, Long. Nitrous oxide was first employed in 1844, by the American dentist, Wells, who employed it for the extraction of teeth. Wells subsequently administered the gas for surgical purposes, and used ether for dental operations in 1845. Ether was first used in England in 1846, and in the following year Simpson, of Edinburgh, used chloroform during childbirth.

The use of these three substances was thus well established by 1885, although the Pharmacopœia only included ether and chloroform; nitrous oxide was not made official until 1932. The only other inhalant anaesthetic to be taken into general use since then is ethylene, which was also described for the first time in the 1932 Pharmacopœia. Obtained from the gaseous products of the cracking of petroleum, ethylene proved an uncertain and somewhat dangerous anaesthetic at first, principally on account of the carbon monoxide it contained. With the stringent purity requirements of the Pharmacopœia, it is now generally regarded as one of the safest anaesthetics for cases attended with risk, since it produces no alteration to the tissues or blood, does not impair liver functions, shows very little effect on renal activity, and may be administered with a large amount (20 per cent.) of oxygen.

The comparatively recently introduced divinyl ether $(CH_2:CH)_2O$, combines the structural similarities of ethylene and ether,

and is considered to be a very safe anaesthetic. Cyclopropane, $C_3H_6$, introduced about the same time, is also very safe, and may be used in quite low concentration.

The field of general anaesthesia has been widened by the introduction of substances which may be administered by injection. These are of two main types, those which are derivatives of barbituric acid, those which may be regarded as cocaine substitutes. Sodium amytal (the sodium salt of ethyl-*iso*-amylbarbituric acid) and nembutal are examples of the first type, the former being particularly useful for operations of short duration, such as may be required for dental work. The first use of cocaine in surgery was made in 1884, when Koller, of Vienna, employed it for operations on the eye. It was not long before investigations were started with the object of producing substitutes which did not suffer from the disadvantages involved in the use of cocaine, notably its decomposition on boiling in aqueous solution, its general toxicity and its habit-forming properties. The attack was along two main lines, the first with the idea of reproducing, in major points, the structure of cocaine. This resulted in the production by Merling in 1897 of the two piperidine derivatives, *a*- and β-eucaine,



Cocaine



*a*-Eucaine



β-Eucaine

the lactate of the latter being included in the 1914 Pharmacopœia as benzamine lactate. The second line of attack, developed by Fourneau, was based on the idea that the alkylamine esters of benzoic acid should possess local anaesthetic properties, and resulted in the development of anaesthetics of the type of amylocaine. In the course of the work the following generalizations were formulated:—Anaesthetic properties are associated with esters of amino-alcohols of the general formula $R_2N(CH_2)nOH$, where n is 2 or 3. Maximum anaesthetic effect is obtained when n is 3, but as these compounds

have also greater toxicity than the lower members, it is generally preferable to use the $\alpha$ $\beta$ aminoalcohols (n = 2) in practice. The esterifying acid must contain an aromatic nucleus; in general benzoic acid is employed, although cinnamic may replace it in some of the simpler compounds, and cinchoninic acid is present in percaine. The amino group should be secondary or tertiary, and may be in an open chain or associated with ring structures. The esterified alcoholic group may be either primary, secondary or tertiary.

Most of these generalizations are exemplified in the following anaesthetics:—

| | |
|---|---|
| Amylocaine | $(CH_3)_2N.CH_2.C$ Me Et.$O.CO.C_6H_5$ |
| Percaine | $(C_2H_5)_2N.CH_2.CH_2.NH.CO.C_9H_5N(OC_4H_9)$ |
| Procaine | $(C_2H_5)_2N.CH_2.CH_2.O.CO.C_6H_4.NH_2$ |
| Butyn | $(C_4H_9)_2N.CH_2.CH_2.CH_2.O.CO.C_6H_4.NH_2$. |

The fact that percaine is a substituted acid amide, instead of an ester, makes little difference because the external configuration of the NH-group very closely resembles that of an oxygen atom. Procaine and butyn differ from the first two in that they are esters of *p*-aminobenzoic acid. The observation that the esters of the amino- and hydroxy-benzoic acids possessed local anaesthetic properties was made by Einhorn and Heintz in 1897, and has led, not only to the modification in procaine and butyn, but also to the inclusion of benzocaine (ethyl *p*-aminobenzoate) and orthocaine (methyl *m*-amino-*p*-hydroxybenzoate) in the Pharmacopœia.

It is probably in the field of such anaesthetics as these that organic chemistry has had its greatest success in application to therapeutics, and, as Fourneau claims, cocaine would probably have no place in medicine at all were it not for the fact that its illicit use is the chief reason for its commercial importance.

Of quite distinct type of basal anaesthetic is avertin, tribromethyl alcohol, $CBr_3.CH_2OH$, introduced by Eichholtz in 1927. The presence of the $CBr_3$-group makes avertin analogous to the chlorine compounds, chloroform, chloral and chlorbutol.

A further application of synthetic organic chemistry to therapeutics has resulted in the development of the branch of science known as chemotherapy. Chemotherapy may be defined as the treatment of disease by chemical substances which have been shown to

be relatively much more toxic to pathogenic organisms than to human or other animal hosts. The subject requires the collaboration of organic chemists, biologists and clinicians. It had its origin in the work of Ehrlich, who had noted that the injection of some dyes into a living animal resulted in the selective staining of certain tissues. In 1891 he observed that the malaria parasite was strongly stained by methylene blue, and thus differentiated from the tissues of the host. This led him to believe that drugs might be discovered which had a sufficiently high affinity for the organisms to kill them without damage to the tissues of the host.

Ehrlich's most successful work in the field of chemotherapy resulted in the introduction of the arsenic group of spirochaeticides. The early use of the sodium salt of *p*-aminophenylarsonic acid under the name of atoxyl, and of its acetyl derivative (arsacetin) was followed by the production of the trivalent arsenic compounds, salvarsan (or arsphenamine) and neoarsphenamine. The serial numbers of these two compounds (the familiar 606 and 914 respectively) give some idea of the lengthy and systematic nature of Ehrlich's work in this field. The inclusion in the Pharmacopœia of the drugs neoarsphenamine and sulpharsphenamine, together with the two pentavalent arsenic compounds, acetarsol and tryparsamide, is sufficient indication of the value of these substances in the treatment of diseases produced by spirochaetes.

Chemotherapeutic investigation has not only moved along this line, but has also been directed towards the discovery of substances which could be effectively employed in treatment of other protozoan diseases, such as malaria and amoebic dysentery, as well as towards the preparation of bactericides.

In the search for antimalarials the discovery of plasmoquin and atebrin is noteworthy, whilst the work of Henry and his collaborators on the modified cinchona alkaloids holds promise of distinct achievement in this field. The search for substitutes for emetine in the treatment of amoebic dysentery has produced some very interesting results in the hands of Pyman, although, from a clinical point of view, little has been achieved.

Greater success has attended the search for bactericides, not only in the well-established field of the phenols, but in other classes of substances as well. Amongst the alkyl resorcinols, hexylresorcinol was shown in 1926 to possess peak activity, having a Rideal Walker

coefficient of 50, whilst more recently 4-*n*-amyl-*m*-cresol has been shown to have phenol coefficients of over 200 when tested on a variety of organisms. The former was introduced into medicine as a urinary antiseptic, and the latter, although of little value in this regard, is a useful antiseptic in the buccal cavity.

The successful treatment of urinary infections by means of the unpleasant ketogenic diet led to the recognition of the importance, in this respect, of the presence of β-hydroxybutyric acid in the urine. The search for suitable hydroxy-acids which could be administered orally, and which were excreted unchanged in the urine, resulted in the introduction of the mandelic acid treatment by Rosenheim in 1935.

In the field of the acridines, Albert, Bradbury and Linnell have carried out some valuable work on the bactericidal activity and the toxicity of various mono- and di-amino derivatives. It has been shown that many of the more recently prepared compounds possess activity of the same order as proflavine and the official acriflavine, but they are very much less toxic. Commercial acriflavine, in fact, has been shown to be the most toxic preparation in this series.

One of the greatest advances within recent years has been the introduction of the sulphanilamide group of bactericides. Sulphanilamide itself (*p*-aminobenzene sulphonamide, $NH_2.C_6H_4.SO_2NH_2$), although prepared early in this century, was not recognized as possessing powerful bactericidal properties until 1935. Attempts to modify this simple substance with a view to improving on it have shown that its activity depends on the presence of an amino group and of a sulphur atom. Removal or duplication of either considerably lowers or destroys the activity, as does also the introduction of other substituent groups into the benzene nucleus. Modification of the amino group by acetylation or by combination with aromatic aldehydes gives products which are, in some cases, more active than the parent substance. 4.4′-Diaminodiphenylsulphone, $NH_2.C_6H_4.SO_2.C_6H_4NH_2$, and some of its derivatives show greater streptococcidal activity than sulphanilamide, but on the whole they are more toxic to the host. Sulphanilamide is of considerable clinical value in treatment of haemolytic streptococci, the meningococcus, the gonococcus and urinary infections of B. coli, and there is some evidence that it may be of value in treatment of pneumonia due to type III pneumococcus and in gas gangrene. Part of the value of the

drug lies in the fact that it is active, in varying degree, against practically all bacteria, distinguishing it from the specific drugs which are used against protozoans, e. g., emetine in amoebic dysentery, quinine in malaria and the arsenicals in the spirochaetal diseases.

The newest of the sciences which we have to consider is biochemistry. With its origin in the synthesis of urea by Wöhler in 1828, the science may be said to have acquired status in 1883, when the first chair of physiological chemistry was established in Strasbourg. Its development was slow, however, until this century, when, by the elaboration of its own special methods and refined technique, it was shown to have an important place in clinical medicine. Since then its rate of progress has been so rapid that it is quite impossible to hazard a guess as to what achievements even the immediate future may hold.

The fields of application of the subject, even so far as we are concerned, are numerous. Firstly, it is placing the practice of medicine on a firm basis, which is not empirical; it has supplied the key to the rational study of normal and pathological living; it has increasing use in diagnosis and the determination of the cause of disease; it is of use, on occasion, in indicating methods of treatment of disease; and it dominates the study of diet in all its aspects. In its application to industry biochemistry has been concerned chiefly with the activity of bacteria, moulds and fungi in producing chemical change, and has resulted in improved methods of preparation of a considerable number of chemical substances, such as citric acid, acetone and butyl alcohol. It is my intention to touch only briefly on a few of these aspects.

The earliest recorded observations which we have on the production of illness through nutritional deficiency were made by Jacques Cartier little more than 400 years ago. Cartier, when in Quebec during the winter of 1535-36, was made acquainted by the Indians with a cure for scurvy, in the form of a decoction made from the leaves of an evergreen. Sour fruit juices were first used late in the sixteenth century by Hawkins for the same purpose, and further references to such use occurred frequently. Lunin, in 1881, recognized that artificial mixtures of fat, carbohydrate, protein, mineral salts and water cannot be used for rearing experimental animals, although milk, which contains all these substances, is adequate for this purpose. Although Lunin concluded that the milk must contain other

essential substances as well as these, it was not until 1906 (and even so the results were not published until 1912) that Hopkins definitely established this fact. The recognition of a third accessory food factor was made by Eijkmann in the study of polyneuritis, an avian condition comparable with beri-beri, which is produced by a diet of polished rice. The use of an alcoholic extract of rice polishings in the cure of beri-beri was reported by Fraser and Stanton in 1907, and in 1911 Funk separated from rice polishings a highly active crystalline, basic nitrogenous substance which he called "vitamine." At this time, then, three accessory food factors were known, one being essential for growth, one for the prevention of scurvy and one for the prevention of beri-beri, and it became customary to call them vitamins, the name being taken from Funk's original word, with the elimination of the final "e," since they are not all amines. Since then, the number of vitamins has been increased to ten or twelve, their functions in maintaining normal health and growth slowly worked out, the constitutions of a number elucidated and several of them have been synthesized.

Vitamin A, synthesized in 1937, is a polyene compound, and may be produced from the plant pigment, β-carotene, by molecular fission, with the addition of two molecules of water. This conversion of β-carotene into vitamin A is one of the few reactions, if not the only one, in vitamin synthesis which the body can accomplish. In addition to its first recognized effect in promotion of growth, the vitamin is essential for maintenance of normal skin resistance to bacterial attack, it is a mutual synergist of vitamin D, it plays an essential part in synthesis of visual purple, and, in its deficiency, degenerative changes may occur in the auditory organs.

The nomenclature of the B-complex has led to much confusion. The first member, vitamin $B_1$, or aneurin, is Eijkmann's original antineuritic vitamin. It was first isolated in pure form in 1926; its constitution has been worked out, and it was synthesized in 1936 by Williams and Cline. In addition to its antineuritic properties, the vitamin has been shown to play an important part in oxidative changes in the brain. The remaining members of the group are commonly referred to as the vitamin $B_2$ complex. This complex consists of at least three factors, and it is in the naming of these that much confusion has occurred. Firstly, it contains one of the flavins, now considered to be riboflavin, but which has also been described

as lactoflavin, vitamin $B_2$ and vitamin G. Secondly, it contains vitamin P or PP, the antipellagra, or pellagra-preventing factor, which is probably closely related to, if not identical with, nicotinic acid; and, thirdly, it contains a factor referred to both as vitamin $B_6$ and vitamin H, which must be added to riboflavin and aneurin to complete the growth promoting activity of the whole vitamin B complex.

Vitamin C, now more commonly referred to as ascorbic acid, was first isolated by Szent-Györgyi little more than ten years ago, and was separated by him in quantity in 1932 from Hungarian capsicum. The proof of its structure was given by Hirst and his collaborators in 1933, and the acid was subsequently synthesized. Although the main function of the vitamin appears to be the prevention of scurvy, a considerable amount of evidence has been accumulated indicating that it may have a special function in enabling the body to resist certain infections.

The proof that rickets is a dietary deficiency disease was given in 1918, when Mellanby showed that the condition could be induced in puppies simply by variation of diet. The recognition of the value of sunlight, and in particular of ultra-violet light, in curing rickets, together with the observation in 1924 by Steenbock, that ultra-violet irradiation of inactive foodstuffs will induce antirachitic properties, led to the production of crystalline calciferol in 1930 by Bourdillon and his collaborators in the laboratories of the Medical Research Council. During the following year the vitamin was produced in quantity by Bourdillon, and also by Windaus in Germany and by Reerink and van Wijk in Holland. The multiplicity of vitamin D activity was quickly recognized on biological grounds, and calciferol was hence named vitamin $D_2$ to distinguish it from the naturally occurring vitamin of cod liver oil. A third highly active crystalline substance ($D_3$) was prepared by irradiation by Windaus in 1936, and almost simultaneously was isolated from tunny liver oil by Brockmann. It is of interest to note that vitamin $D_3$ appears to be the only active substance present in halibut liver oil. Windaus has since (1937) prepared a fourth crystalline D vitamin by irradiation. The main functions of vitamin D are twofold. Firstly, it is essential for calcium absorption from the intestine, and hence, indirectly, for the absorption of phosphorus, since in its deficiency, the increased calcium concentration results in the precipitation of phosphorus as cal-

cium phosphate. Secondly, it has a specific function in the production of the phosphatase enzyme, which converts organic phosphates into inorganic phosphate, in which form the phosphorus is available for calcification.

Vitamin E was first described in 1922 by Evans and Bishop, who showed that rats would grow to maturity on a diet containing vitamins A, B and D, but would not reproduce. Although two active alcohols, α- and β-tocopherol, have been isolated from wheat germ oil by Evans and his collaborators, it does not yet appear possible to recognize either of these as the pure vitamin. In addition to the direct effect of fertility, it has recently (1937) been shown that deprivation of vitamin E leads to thyroid and anterior pituitary deficiency.

The latest addition to the vitamin register was made in 1934, when Dam and Schonheyder described a deficiency disease in chickens characterized by a tendency to haemorrhage, anaemia and a prolonged blood-clotting time. This factor, known as vitamin K, has been prepared in highly concentrated form, and it would appear possible that the vitamin may be present as a prosthetic group in the prothrombin molecule.

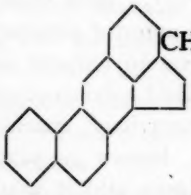
It is not my intention to review the progress which has occurred in our knowledge of either the duct or ductless glands of the body. Such a review would entail a survey of practically the whole of our exact knowledge of these organs, a task in itself beyond the scope of an address such as this. As far as the ductless glands are concerned, I would commend to your notice the already mentioned presidential address given by Stanton to this section two years ago.

Before leaving the subject of the contributions of biochemistry to medicine, I should like to direct your attention to the question of the sterols and related compounds.

Within the last decade, the knowledge of this large group has advanced tremendously, and the presence of similar structures in such a variety of substances as the sterols, bile acids, vitamin D, and possibly vitamin E, the sex and adrenal hormones, the cardiac aglycones, etc., is most significant, the more so because certain substances closely related to these have been shown to be powerfully carcinogenic. The close relationship between these substances and the relative ease of converting one to another, suggest the possibility that some simple upset in basal metabolic changes may be all that is

necessary to bring about the production of powerful cancer-producing substances in the body.

The carcinogenic properties of soot were first recognized in 1775 through the high incidence of cancer of the skin in chimney sweepers. The same type of cancer is prevalent amongst workers with coal tar, mineral lubricating oils, etc., and it has been recognized recently that certain anthracene derivatives are characteristic constituents of such materials. The most powerful of these substances are derivatives of 1.2-benzanthracene, methylcholanthrene being the most potent carcinogenic substance known.




Methylcholanthrene.

Derivatives of cholanthrene may be formed from certain sterol compounds, and Wieland has actually converted cholic and deoxycholic acids into a reduced derivative of methylcholanthrene. It is known that the body can effect the necessary dehydrogenation which would convert this substance into methylcholanthrene itself. This fact gives food for speculative thought in the question whether the changes involved in the production of methylcholanthrene from bile acids may not occur in the body under conditions of disordered metabolism. The question is a difficult one, and, although an early answer does not seem possible, it is not expecting too much to hope that the solution will ultimately be discovered.

Finally, mention must be made of some of the contributions of bacteriology to medicine. Not a new science, since it had its birth in the observation of bacteria by Leeuwenhoek in 1675, bacteriology as we now know it has developed mainly within the last sixty years. The germ theory of disease goes back at least to the middle of the sixteenth century to the Veronese physician, Fracastoro, but, although Leeuwenhoek's observations provided some evidence for the existence of Fracastoro's seminaria or seeds of disease, these early ideas were lost sight of, and were not rediscovered until after the middle of the nineteenth century, through the work of Pasteur, Lemaire, Davaine and others.

The production of an immune condition following an attack of an infectious disease was recognized by the Turks, and led to the practice of inoculation of healthy individuals with pus taken from smallpox pustules to give protection against the disease during epidemics. The practice was introduced into England in 1718 by Lady Mary Montagu, and spread to the rest of Western Europe. The inoculated disease was usually mild in type, but at times was severe, or even fatal. A great advance in smallpox immunization was made by Jenner in 1796 with the introduction of inoculation with the pus taken from the vesicles of cattle suffering from vaccinia or cowpox. Such vaccination was made compulsory in England about 1850.

One of the earliest of the pathogenic organisms to be described was *B. anthracis,* which was observed by Pollender in 1849 in the blood of animals dying from splenic fever. The observation was repeated a year later by Davaine, and in 1857 the organisms were found in the blood of a man suffering from anthrax. Davaine gave everything but absolute proof that they were the cause of anthrax, the complete demonstration of specificity being made subsequently by Koch. Descriptions of other organisms followed slowly until about 1880, when a period of considerable activity in this field developed, lasting until the end of the century. The use of solid culture media, introduced by Koch in 1882, contributed in no small way to the isolation of pure cultures of organisms and to the proof of specificity in many cases. *B. typhosus* was isolated in 1880 by Eberth, and was cultivated in 1884 by Gaffky. The presence of staphylococci in pus was demonstrated by Pasteur in 1880; they were grown in pure culture in 1883, and proof of specificity in some forms of wound suppuration and of osteomyelitis followed in 1884. Streptococci were distinguished from staphylococci during the same period. The diphtheria organism, long known as the Klebs-Loeffler bacillus, was described by Klebs in 1883 and cultivated by Loeffler the following year. Other important discoveries during this period include *B. tuberculosis* (Koch, 1882); *Vibrio cholerae,* the spirillum of Asiatic cholera (Koch, 1883); the pneumococcus (1884); the meningococcus, observed in 1884 and cultivated by Weichselbaum in 1887; *B. enteritidis* (Gaertner, 1888); *B. tetani* (Kitasato, 1889); *Pasteurella pestis* (independently by Kitasato and Yersin, 1894) and *B. botulinus* and *B. paratyphosus,* both of which were discovered in 1896.

After Jenner's discovery there were no further advance in the field of immunology until after 1880. From his idea that smallpox and cowpox were produced by the one organism, and that vaccination with vaccinia virus was simply inoculation with an attenuated organism, Pasteur developed a method in 1881 of preparing cultures of *B. anthracis* of low virulence, and, with such cultures, successfully inoculated sheep against anthrax. This, and other work, strengthened the belief that living organisms were necessary to procure immunization, but it was subsequently shown that immunity is also obtained by inoculation with dead bacteria, with bacterial cell substances, or, as Salmon and Smith demonstrated with hog cholera in 1886, with filtrates from broth cultures.

Apart from certain cases of natural insusceptibility, immunity to bacterial exotoxins depends on the presence in the blood stream of antitoxins which exert a specific neutralizing action on the toxins. The antibodies may have been acquired naturally, as a result of past infection; they may have been produced in response to inoculation with unmodified or modified toxin; or they may have been obtained by transfer of serum from an immune to a susceptible host. The first observations of this nature were made in 1890 by Behring and Kitasato, who showed that the sera of animals which had received repeated, graded doses of tetanus or diphtheria toxin acquired the property of specifically neutralizing these toxins, and would, if injected into a second animal, render the latter insusceptible of what would otherwise be a fatal dose of the toxin.

Since then a considerable number of antitoxic sera have been prepared and used either for prophylactic or therapeutic purposes. Amongst those included in the Pharmacopœia, in addition to diphtheria and tetanus antitoxins, are those which neutralize the toxins of *B. dysenteriae* (Shiga), *Diplococcus pneumoniae* (types I and II), *Staph. aureus, Clostridium* (*or B.*) *Welchii* (*B. perfringens*), *Cl. oedematiens* and *Cl. septique* (vibrion septique).

The first demonstration of antibacterial, as distinct from antitoxic, immunity was made by Pfeiffer in 1893-94. Pfeiffer showed that a guinea pig could be immunized against *Vibrio cholerae,* so that injection of a lethal dose of living organisms could be made with impunity. The serum of the animal, however, had no power to protect the animal against an injection of dead vibrios; in other words, its action was purely antibacterial, and not antitoxic.

In addition to the toxin-antitoxin reaction, and to the lytic action observed by Pfeiffer in his work on *V. cholerae* and antibacterial immunity, further antigen-antibody reactions were soon recorded. The phenomenon of agglutination was described by Grüber and Durham in 1896, that of precipitation by Kraus in 1897, haemolysis by Bordet in 1898, complement fixation by Bordet in 1901, opsonic action by Wright in 1903, and bacteriotropic action by Neufeld and Rimpau in 1904. The view that these antibodies—the antitoxins, lysins, agglutinins, precipitins, complement-fixing antibodies, opsonins, etc.—are different substances, was held for many years. It is now generally accepted, however, that the different antibody-antigen reactions do not indicate the existence of different antibodies, but are simply caused by the one antibody doing different things. Thus precipitation is recognized as a general form of reaction between all antigens and antibodies; precipitation and complement fixation have been shown to be essentially identical; and, further, the union of antigen and antibody on the surface of a bacterial cell is known to sensitize the cell to the flocculating action of electrolytes, to the lytic action of the complement, and to the phagocytic action of the leucocytes.

The phenomenon of transmissible bacterial lysis was described independently by Twort in 1915 and d'Herelle in 1917. The intestinal fluid of a person suffering for some days from dysentery, if filtered through a bacterial filter, was shown by d'Herelle to possess the power of dissolving dysentery organisms growing in another culture medium. The addition of this second liquid to a further culture produces the same effect, and it increases in strength with every repetition. D'Herelle considered that the active factor was an ultramicroscopic bacterial parasite, which he called a bacteriophage. Whether this is so, or whether the lytic agent is some active substance, elaborated by the bacteria themselves, is immaterial to the consideration of the possible value of the bacteriophage in therapy. There is no difference of opinion concerning the *in vitro* reaction, but the recorded observations *in vivo* make out a strong presumptive case against the bacteriophage as an effective therapeutic agent, since consistently negative results have been returned by the majority of observers. There is no obvious explanation of this great difference in behavior, although it may be that the lytic action of the bacteriophage is inhibited by the colloids of the body fluids. Some support

of this view is given by the fact that colloids such as agar and gelatin will inhibit bacteriophage lysis *in vitro*.

I have tried to give you some glimpses of the progress that has been made during the last half-century in pharmaceutical science and those branches of knowledge related to pharmacy. If I have attempted too much, I would ask your forgiveness, for, regarding the advances made during this period, and knowing the intense activity in these fields, I feel sure that this is the last occasion that a review of this nature will be attempted. To foretell the future is impossible, but we may be certain that the acquisition of fresh knowledge will not slacken, for man's inquisitiveness and ingenuity appear limitless, and nature's secrets are only beginning to be unfolded.

# ABSTRACTS FROM AND REVIEWS OF THE LITERATURE OF THE SCIENCES SUPPORTING PUBLIC HEALTH

**Bacteriology** . . . . **Louis Gershenfeld, B. Sc., Ph M.**
**Biology** . . . . . **Marin S. Dunn, Ph. D.**
**Chemistry** . . . . . **Arthur Osol, Ph. D.**
**Pharmacy** . . . . . **E. Fullerton Cook, Ph. M.**
**and their assistants**

**Radioactive Iron and Its Metabolism in Anemia.** P. F. Hahn, W. F. Bale, E. O. Lawrence and G. H. Whipple. *J. Exp. Med. 69,* 739 (1939). The authors made use of radioactive iron prepared by bombarding the $Fe^{58}$ iron isotope with deuterons. This substance behaves physiologically as ordinary iron but due to its slow decay (half-life period forty-seven days) with the emission of free electrons its presence can be quantitatively evaluated by the use of a Geiger-Müller counter.

The complexity of iron metabolism is well known and many past experiments are of questionable significance since ordinary analyses fail to differentiate between iron recently administered and that already present in various body tissues. Furthermore, due to the difficulty of iron analyses, quite often the results obtained could easily have been due to errors in the analytical results.

In this initial investigation the authors made the following findings:

I. There is an apparent ability in the dog to discriminate physiologically insofar as the amount of iron absorbed is concerned. When there is a distinct need for the element as in anemia a fair quantity will pass from the gastro-intestinal tract into the blood stream. When the body reserves of iron are ample very little is assimilated.

II. The plasma is the site of transportation of iron from the intestinal tract to the point or points at which it is further utilized. The absorption as indicated by plasma iron changes increases shortly after feeding to a peak and drops off quite rapidly. Absorption from a given dose of iron probably is complete in the dog at the end of eighteen hours.

III. The appearance of radio-iron in the red cell is very rapid. If an anemic dog is fed neutral iron the earliest time in which it appears in the blood stream as shown by the red cell surge into the circulation is about three to five days. In the case of radio-iron it could be demonstrated in the red cells in appreciable amounts in a few hours.

IV. The importance of liver and bone marrow in iron metabolism was confirmed.

Tables and graphs recording the experimental results accompany the article. L. F. T.

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**The Effect of pH on the Bactericidal Properties of Commercial Antiseptics.** W. A. Bittenbender, E. F. Degering and P. A. Tetrault. *J. Ind. & Eng. Chem. 31,* 742 (1939). Phenylmercuric nitrate, merthiolate, metaphen, mercurochrome, tincture of iodine, phenol, hexylresorcinol and acriflavine were studied under controlled conditions of pH with respect to their bactericidal properties against Staphylococcus aureus and Escherichia coli. Metaphen and merthiolate could not be adjusted and acriflavine gave negative results at the concentrations tested. All the others showed increased potency with an increase in the hydrogen-ion concentration of the solution. Phenyl mercuric nitrate, for example, is effective in a dilution of 1-10,000 at pH 7 (S. aureus) while at pH 3 its effectiveness is ten times as great. At a pH of 4 phenol is 25 per cent. more effective than at pH 7.

The results indicate that, except for such interfering factors such as change in solubility or instability, these diversified antiseptics show a definite increase in effectiveness with an increase in the hydrogen-ion concentration. This is in agreement with the "hydrogen-ion effect" postulated by Goshorn, Degering, and Tetrault (*J. Ind. & Eng. Chem. 30,* 646 (1938)) in their studies of the phenylalkanoic acids. The results do not confirm the statement of Keysser and Ornstein (*Klin Wochschr. 5,* 404 (1926)) that "antiseptics are most effective at some definite pH which is different for each group of antiseptics." The results clearly indicate that the "hydrogen-ion effect" increases progressively up to a maximum for benzoic acid, the phenyl alkanoic acids, phenyl mercuric nitrate, merthiolate, tincture of iodine, hexylresorcinol, phenol, closely related compounds and some inorganic salts.

L. F. T.

**The Determination of Formaldehyde in the Presence of Methenamine.** J. Büchi. *Pharm. Acta Helv. 13,* 132 (1938), through *Quart. J. Pharm. & Pharmacol. 12,* 119 (1939). A method for the determination of small quantities of formaldehyde in the presence of methenamine such as may be produced in the sterilization of methenamine solutions depends on the reduction of an alkaline mercury solution by formaldehyde. Five cc. of a reagent (made by combining 10 gm. mercuric chloride, 25 gm. of potassium iodide and 40 cc. of 10 N. sodium hydroxide in 100 cc.) are mixed with 20 cc. of a methenamine solution (10-40 per cent.) in a stoppered centrifuge tube. After standing for five minutes the mixture is centrifuged and the deposit of mercury is washed several times with water. It is then stirred up with 5 cc. of 2 N. acetic acid and 5 cc. of N/10 iodine. When all the mercury is dissolved the excess iodine is titrated back with thiosulfate. Each cc. N/10 iodine corresponds to 0.001501 gm. of formaldehyde. L. F. T.

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**The Absorption and Excretion of 2-Sulfanilyl-Aminopyridine (Sulfpyridine).** E. J. Baines and R. Wien. *Quart. J. Pharm. & Pharmacol. 12,* 4 (1939). Since Whitley (*Lancet, Lond. 1,* 1210 (1938)) first showed 2-sulfanilyl-aminopyridine (M. & B. 693) to possess antipneumococcal properties far superior to those of any other drug, as well as being active against hemolytic streptococcus and meningococcus, considerable has been written relative to its toxicology, mode of action, etc. In view of the use of this new substance in clinical practice it is important that there should be some knowledge of its absorption and excretion in animals as well as in man. Such information helps the clinician to control the dosage so as to maintain an optimal concentration in the blood. The authors have investigated this subject and have reported their results, which are briefly summarized as follows: In animals (mice, rabbits and dogs) and human subjects absorption of the drug from the gastro-intestinal tract was rapid, despite its sparing solubility in water (about 1-1000); the drug appeared in the blood within one hour from the time orally administered. In rabbits a concentration of about 1 in 10,000 was produced by 0.5 mgm. per gm., and in mice doses above 5 mgm. per gm. resulted

in a blood concentration of about 1 in 3000. In man, after a single dose of 2 gm. there was a blood concentration of 1 in 25,000, while repeated doses of 1 gm. produced a blood concentration of about 1 in 10,000.

The drug appeared in the blood of rabbits in a greater concentration as the free amino body than as the conjugated form. Determinations of free amino body in serum and corpuscles showed that all the free amino body was distributed in the serum. The concentration of free amino body in the cerebrospinal fluid of dogs was about 70 per cent. of that found in blood.

The drug was excreted almost entirely in the urine. After the ingestion of 1 gm. by a normal adult the substance was detected in the urine within one hour and almost the whole dose was excreted within fifty hours. One-half the drug was present in the urine as the acetyl derivative, the other half being unchanged.

L. F. T.

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**The Effect of a Wide Range of Doses of Posterior Pituitary Extract on the Retention of Added Water in Birds and Mammals.** E. M. Boyd, N. D. Garand and R. J. Livesey. *Quart. J. Pharm. & Pharmacol. 12,* 19 (1939). When water is administered to normal unanesthetised birds and mammals there follows a diuresis which is known as a water diuresis and which is inhibited or deferred by the simultaneous injection of suitable extracts of the neurohypophysis. The authors have studied the effect of varied doses of pituitrin on white rats, guinea-pigs and cockerels which were deprived of water for fifteen to eighteen hours, and then given 5 per cent. of their weight of water by stomach tube.

In very small doses pituitrin stimulated loss of added body water. In medium doses, pituitrin produced retention of added body water and an optimal dose could usually be found which caused almost complete retention of added body water. In very large doses, pituitrin again stimulated relatively or absolutely the loss of added body water.

L. F. T.

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**Alleged Clinical Importance of Buffered Local Anesthetic Solutions.** M. L. Tainter, A. H. Throndson and S. M. Moose.

*J. A. D. A. 26,* 920 (1939). Frequent claims are made relative to the superior qualities of dental anesthetic solutions which are buffered to the pH of the tissues. Theoretically, of course, it is desirable that nothing be injected which does not have the same hydrogen-ion concentration as the fluids of the body. In actual practice, however, it is a question whether departures from the physiologic state, which may be encountered in otherwise desirable anesthetic solutions are great enough to affect the clinical value or desirability of such solutions. If not then the greater difficulty involved in manufacturing such buffered solutions plus their greater cost to the user would not seem to be warranted.

The authors report on an investigation of the problem conducted in such a manner as to insure the elimination of personal impressions or other subjective factors which would vitiate the reliability of the results.

A series of 579 injections of neutral buffered (pH 7.4) and acid unbuffered local anesthetic solutions of procaine hydrochloride were made under conditions of blind testing in which the operators did not know the composition of the solutions that they were using. Their observations of the important factors in the local anesthesia were tabulated and computed independently to determine, if possible, significant differences between the two solutions.

There were practically no differences between the two solutions which would indicate a probable advantage of one over the other. The volumes required, the speed of onset and duration of anesthesia and the effects on the circulation and respiration were all practically identical. Similarly, there was no definite difference in the number of cases in which complete anesthesia was secured, nor in the cases in which the injection of the anesthetic solution caused pain. The amount of bleeding was also not definitely affected by the choice of solution.

Such side actions as nervousness, perspiration, tremors and fainting occurred with about equal frequency with the two solutions. If anything, there was a very slight difference in favor of the unbuffered solution.

Late effects of the local anesthetic injections observed on subsequent days also showed no significant difference in favor of the buffered solution. There was more swelling at the site of the injection.

trismus and dry socket after injection of the buffered solution, but there were less painful injection sites.

The operators themselves recorded satisfaction with the local anesthesia of both solutions and indicated complete satisfaction in 91 per cent. of cases when the acid unbuffered solution was used, but in only 81.9 per cent. of those injected with the neutral buffered solution.

Accordingly, buffering local anesthetic solutions to about the hydrogen ion concentration of the tissues does not result in a clearly demonstrable and unmistakable improvement in effectiveness and clinical desirability of the anesthetic solution. Therefore, there is no good reason why buffered solutions should be used, in view of the greater difficulties of maufacture and of distribution. The tissues are so well buffered that injections of the small quantities of local anesthetic solutions currently used in dentistry are not sufficient to modify the local pH to an extent great enough to produce any clinically significant alteration in the local or systemic responses.

L. F. T.

# BOOK REVIEWS

**Done by persons, unafraid to upbraid, but perfectly willing to give praise where praise is really due.**

**The American Way of Life.** George E. Sokolsky, with an introduction by Fulton Oursler. Published by Farrar and Rinehart, New York City. 180 pages and index. Price, $2.

Gathered from the timed pages of our cosmopolitan contemporary, the magazine *Liberty,* this volume endeavors to tell us that we here in America have "achieved the most comfortable, the most convenient, the freest life known to man", that "the American way, in spite of wars, depressions, confusing policies and politics, provides a more secure, a more comfortable, a more convenient, and particularly a freer way of life than any other on earth", and that "each man's work brings him more in America, in terms of goods and services, than is available in any other country",—all through the courtesy of that mass educator of educators, advertising.

Mr. Sokolsky tells us, in his best romantic style, how oranges were once curios but are now common commodities; how our foodstuffs in general are less expensive and more edible, enticing and convenient today than they were a century ago; how electricity, radio, tomatoes and soup (all in one chapter) help make the United States better for living; how milk and dairy products are cleaner, more palatable and healthful now than ever before; and how automobiles are lower in price yet higher in endurance today—again, through the good offices of advertising.

He continues to tell us, most interestingly and quite convincingly, for he uses unimpeachable facts, of the origin and development of modern cereals so temptingly available for our breakfasts; of the self-imposed standards created and adopted generally by the cosmetic industry so that every girl can safely and economically be a queen; how even the most rural habitation can be made most habitable through modern advances in furnishings and electrical appliances; how America is so rich in everything, thereby affording, as in no other country, the opportunity for the triumph of private enterprise (what, no complaint about taxes?); the remarkable and inimitable freedom of our press; consumers' protective movements; and various yardsticks indicating unanimously that America is the best country in which to live, so long as advertising can continue to tell us everything about everything.

The chapter of most interest to readers of the AMERICAN JOURNAL OF PHARMACY, however, is one entitled "The Medicine Chest." Witness the inaugural words—"The old-fashioned apothecary was an interesting citizen. He mixed potions, filled capsules, fixed salves and prepared tinctures. He was also the town's gossip and everybody's friend. He had time—lots of time—because he had nothing else to do. He has been succeeded in American life by the druggist: seller of ice cream, breakfasts, lunches, sundries, rubber goods, books, cigars and cigarettes, electrical appliances, watches and clocks." Fortunately for Mr. Sokolsky, and also for his hapless victims, thrown ruthlessly into one crude category like soap or automobile tires, of which there are very good and very bad examples, he continues, "But the druggist has not lost the art of distilling and making medicines." Reading further, we learn that the druggist is overworked and underpaid. He could not possibly compound medicines as accurately as do large manufacturing plants. He dispenses innumerable prescriptions simply by scraping off manufacturers' labels and affixing his own. In doing this, he need not carry an expensive stock of samples for prescription compounding (sic.) Thus there is no substitution or omission of important ingredients. And all of these "benefits" to druggist and customer come through almighty advertising to profession and laity.

Read now the punch paragraph of the chapter—

> "Some of these proprietary medicines find their way into the National Formulary and the United States Pharmacopœia, not under their advertised trade names but under their ingredients. And so you can go to a physician and he can give you a prescription and the druggist can fill it and you can have all that special cost for exactly the same article—just because somebody told you not to use an advertised medicine. If you like to waste your money that way, that's your affair. I don't."

It is quite urgently suggested that Mr. Sokolsky, and his editor-employer-introducer, Mr. Oursler, now leave their sancta sanctora and hie themselves to a real apothecary shop, which, thank goodness, is still present in increasing numbers, and study the stock of prescription items, proprietaries, invoice prices, prescription prices, overhead and the multifarious other factors which enter into modern pharmaceutical practice, and then run, not walk, back to their typewriters for the express purpose of writing another book, this time one that portrays the truth in *every* chapter.

J. E. KRAMER.